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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Steinemann, T. L. *et al.*	§	**ART UNIT: 1502**
	§	
FILED: May 20, 1996	§	
	§	**EXAMINER:**
SERIAL NO.: 08/580,384	§	**Kishore, G**
	§	
FOR: Novel Ophthalmologic Uses of Protein C	§	**DOCKET: 5715D**
	§	

17/Appeal Brief (3) fee att.

The Assistant Commissioner of Patents and Trademarks
BOX AF
Washington, DC 20231

ATTENTION: Board of Patent Appeals and Interferences

APPELLANT'S BRIEF

This Brief is in furtherance of the Notice of Appeal filed in this case on June 14, 1999. The fees required under 37 C.F.R. §1.17(f) and any other required fees are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

In accordance with 37 C.F.R. §1.192(a), this Brief is submitted in triplicate.

INDEX OF SUBJECT MATTER

I. REAL PARTY IN INTEREST

The real party in interest is the University of Arkansas, the Assignee, as evidenced by an Assignment recorded in the Patent & Trademark Office at Reel 7177, frame 0346, on August 8, 1994.

II. STATUS OF THE CLAIMS

Originally, claims 22-29 were filed in this divisional application. Claim 22 has been amended. Pending claims 22-29 are being appealed, of which claim 22 is an independent claim.

III. STATUS OF AMENDMENTS

Claim 22 was amended in the response filed June 13, 1997 and the amendment was acknowledged. All pending claims are shown in Appendix A.

IV. STATEMENT OF RELATED APPEALS AND INTERFERENCES

To Appellant's knowledge, the pending appeal of related application Serial No. 08/237,649 may directly affect or be directly affected by the present appeal.

V. SUMMARY OF THE INVENTION

Formation of intraocular fibrin subsequent to ocular surgery, inflammation, hemorrhage, or trauma is a serious medical problem (page 1, lines 15-17). The present invention provides a method of reducing intraocular fibrin comprising the administration of a pharmacologically effective dose of protein C to an individual having elevated levels of intraocular fibrin (Page 6, lines 7-10). The present invention also encompasses a method of reducing ocular inflammation comprising the administration of a pharmacologically effective dose of protein C to an individual having said ocular inflammation. Representative examples of ocular inflammatory states selected from the group consisting of uveitis, including or patients with inflammatory glaucoma, immediate post-operative of

post-traumatic states, i.e., patients who have undergone glaucoma filtration surgery of in patients who have had corneal transplant surgery (Page 8, Lines 9-16).

VI. ISSUES

A. 35 U.S.C. §103

(1) Whether claims 22-27 are obvious over **Galin** *et al.* (U.S. Patent No. 4,240,163, December 23, 1980) or **Iverson** *et al.* (*Archiv. Opthamol.*, 109:405-409, March 1991) in combination with **Bang** *et al.* (U.S. Patent No. 5,151,268, September 29, 1992) and **Esmon** *et al.* (U.S. Patent No. 5,147,638, September 15, 1992) under 35 U.S.C. §103(a).

(2) Whether claims 28-29 are obvious over **Galin** *et al.* (U.S. Patent No. 4,240,163, December 23, 1980) or **Iverson** *et al.* (Archiv. Opthamol., 109:405-409, March 1991) in combination with **Bang** *et al.* (U.S. Patent No. 5,151,268, September 29, 1992) and **Esmon** *et al.* (U.S. Patent No. 5,147,638, September 15, 1992) and further in view of **Stocker** *et al.* (U.S. Patent No. 4,849,403, July 18, 1989) under 35 U.S.C. §103(a).

VII. GROUPING OF CLAIMS

The rejected claims stand or fall together.

VIII. ARGUMENTS

A. 35 U.S.C. §103

(1) In the Office Action mailed January 13, 1997, claims 22-27 were rejected as obvious under 35 U.S.C. §103(a) over the combination of **Galin** *et al.* (U.S. Patent No. 4,240,163, December 23, 1980) or **Iverson** *et al.* (Archiv. Opthamol., 109:405-409, March 1991) with **Bang** *et al.* (U.S. Patent No. 5,151,268, September 29, 1992) and **Esmon** *et al.* (U.S. Patent No. 5,147,638, September 15, 1992). This rejection has been maintained in the Final Office Action mailed October 14, 1997 and the Advisory Action mailed February 3, 1998. This rejection is respectfully traversed.

Galin teaches that the anticoagulant heparin inhibits blood clotting and inflammation of the eye, while **Iverson** discloses that intraocular fibrin formation during vitrectomy is inhibited by heparin. Neither **Galin** nor **Iverson** teach the use of protein C.

Esmon discloses that activated protein C reduces the production of tumor necrosis factor (TNF) thereby inhibiting TNF-induced inflammatory changes in endothelial cells. **Bang** teaches that protein C enhances the lysis of fibrin and that activated protein C has a wider therapeutic index than anticoagulant such as heparin. This make protein C more likely to be effective and less likely to cause complications than heparin. Therefore, the Examiner argues that based on the combination of **Bang** and **Esmon**, it would be obvious to replace heparin with protein C in the inventions of **Galin** or **Iverson** to obtain the instant invention. The Appellants respectfully disagree.

Galin *et al.*, "Medicament Coated Intraocular Lens," discloses an ophthalmic prosthetic device to be surgically implanted in the eye in replacement of a cataracteous lens. The lens is coated with a medicament to reduce problems caused by trauma to the eye during the surgical implantation of the lens. Heparin is included in the medicament as an anticoagulant and anti-inflammatory agent. **Iverson** *et al* teaches that low molecular weight heparin may be infused into the eye to prevent intraocular fibrin formation during eye surgery. However, as admitted by the Examiner, neither **Galin**

nor **Iverson** suggest protein C as an alternative to heparin in the ocular environment.

Bang *et al.* provides DNA encoding human protein C and an assay for protein C activity. Bang suggests that human protein C will be a useful replacement for heparin in a wide variety of thrombotic conditions "including deep vein thrombosis, pulmonary embolism, peripheral arterial thrombosis, emboli originating from the heart or peripheral arteries, acute myocardial infarction, thrombotic strokes, and disseminated intravascular coagulation (column 19, lines 4-11)." **Bang** also suggest that protein C is more useful in the treatment of such conditions because of the lower likelihood of bleeding complications. However, **Bang** makes no observations regarding the applicability of protein C to inflammatory conditions. **Bang** does not even discuss the effect of protein C on inflammatory complications or symptoms resulting from the thrombotic diseases discussed therein.

Furthermore, **Bang** limits the administration of protein C to parenteral methods and other methods which "ensure its delivery to the blood stream in an effective form" (column 21, lines 53-55). However, the ocular environment of the instant invention is

normally isolated from the blood stream by the blood-aqueous barrier. In contrast to Bang, the instant invention utilizes other methods including topical administration, subconjuctival injection, intracameral injection, and intravitreal injection. **Bang** teaches the protein C can "enhance the lysis of fibrin in human whole blood and suggests that this effect is mediated through interaction with a newly discovered inhibitor of tissue plasmogen activator." **Bang** does not teach that this inhibitor would be present in the aqueous humor, the vitreous humor, or the optical environment in general. Thus, **Bang** fails to provide a reasonable expectation that protein C would be effective in the ocular environment.

Esmon et al. teaches the treatment of cancerous tumors using an inhibitor of protein C in combination with a cytokine such as tumor necrosis factor. The Examiner states that **Esmon** teaches that TNF causes inflammatory changes at the endothelial cells and stimulates microvascular thrombosis. **Esmon** also discloses that activated protein C reduces TNF production. However, **Esmon** does not teach that the presence of TNF in the ocular environment. **Esmon** provides no evidence that the biochemical cascade of events described therein occurs in either the aqueous or vitreous humor of

the eye. Moreover, **Esmon** utilized canines to determine the effect of protein C on tumor inhibition. **Esmon** admits the "natural fibrinolytic system of dogs is very potent" (column 17, line 17) which results in a blood plasma environment unlike that in human. Therefore, the **Appellants** submit that very little can be gleaned from **Esmon** in relation to the instant invention.

The Examiner has previously argued that "the cascade of chemical reactions and the subsequent fibrin formation is generally a vascular phenomenon and not dependent on the tissue." However, the ocular environment differs from other tissues in that it is isolated from the blood stream by the blood-aqueous barrier. Therefore, because of this special circumstance, a vascular phenomenon that may apply in other tissues does not necessarily apply to the ocular environment. Furthermore, there are many reasons why a cascade reaction may be disrupted in a tissue specific manner such as the presence of tissue specific inhibitors or the tissue specific absence of a required cofactor. The specific features of the ocular environment were unknown prior to the instant invention. In particular, the effectiveness of protein C in reducing inflammation in the eye had not been demonstrated prior to the

instant application (Example 8 of the instant application). Therefore, no combination of the cited references would indicate that protein C would be effective in treating inflammation in the ocular environment.

Taken together, **Galin**, **Iverson Bang**, and **Esmon**, provide no information on whether protein C is active in the ocular environment, specifically the aqueous or vitreous humor of the eye. No combination of the above references suggests the ophthalmologic application of protein C described in the instant invention. Therefore, the above of combination of references cannot anticipate that a treatment encompassing protein C will be effective in the ocular environment. For this reason, any combination of **Galin**, **Iverson, Bang**, and **Esmon** fails to render claims 22-27 obvious. Therefore, the Appellants respectfully request that the decision of the Examiner should be reversed, and that claims 22-27 be allowed.

(2) In the Office Action mailed January 13, 1997, claims 28-29 were rejected as obvious under 35 U.S.C. §103(a) over the combination of **Galin** *et al.* (U.S. Patent No. 4,240,163,

December 23, 1980) or **Iverson** *et al.* (Archiv. Opthamol., 109:405-409, March 1991) in combination with **Bang** *et al.* (U.S. Patent No. 5,151,268, September 29, 1992) and **Esmon** *et al.* (U.S. Patent No. 5,147,638, September 15, 1992) and further in view of **Stocker** *et al.* (U.S. Patent No. 4,849,403, July 18, 1989). This rejection has been maintained in the Final Office Action mailed October 14, 1997 and the Advisory Action mailed February 3, 1998. This rejection is respectfully traversed.

The argument that combination of **Galin** or **Iverson** with **Bang** and **Esmon** makes the use of protein C to inhibit inflammation in the eye obvious has been discussed in detail above. None of the above references disclose the use of protein S in addition to protein C. **Stocker** teaches that protein S augments the action of protein C. Therefore, the Examiner argues the combination of **Galin** or **Iverson** with **Bang**, **Esmon** and **Stocker** makes obvious the combined use of protein C and protein S to treat inflammation in the eye. The Appellants respectfully disagree.

The teaching of **Stocker** *et al.* regarding protein S is limited to "the action of protein C is potentiated by protein S, phospholipid, and calcium and is inhibited by a specific inhibitor

contained in the plasma" (Column 1, lines 16-18). **Stocker** does not provide any observation on the activity of either protein C or protein S in the ocular environment. In particular, no indication is provided regarding whether the specific inhibitor mentioned above is present in the ocular environment. Furthermore, nothing in **Stocker** either alone or in combination with **Galin, Iverson, Bang** and **Esmon** would indicate to one of skill in the art whether protein C would be active in the eye and thus effective in an ophthalmic treatment.

Stocker *et al.* describes a method for assaying protein C and an "activator preparation" for activating protein C by converting the inactive zymogen form of protein C into the active form. **Stocker** *et al.* indicates that the activated protein C caused no clotting within 10 minutes, and when tested on a non-heated human fibrin plate resulted in no fibrinolysis within 15 hours (Column 6, lines 55-58). By contrast, the instant invention teaches the utility of protein C in fibrinolysis. Thus, **Stocker** actually teaches away from the instant invention

Galin, **Iverson**, **Bang**, and **Esmon** provide no information on whether protein C is active in the ocular

environment, which is separated from the bloodstream by the blood-aqueous barrier. While **Stocker** may indicate that protein C activity is potentiated by protein S, **Stocker** provides no information on the activity of either protein C or protein S in the ocular environment. Therefore, no combination of **Galin**, **Iverson Bang**, **Esmon** and **Stocker** suggests that protein C, protein S or any combination thereof would be effective in treating ocular inflammation. As the above combination or references clearly fails to make the instant invention obvious, the Appellants respectfully request that the decision of the Examiner should be reversed, and that claims 28-29 be allowed.

Respectfully submitted,

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CLAIMS ON APPEAL

22. A method of reducing intraocular inflammation comprising the administration of a pharmacologically effective dose of Protein C to reduce said intraocular inflammation to an individual having said inflammation.

23. The method of claim 22, wherein said Protein C is selected from the group consisting of human Protein C and activated Protein C.

24. The method of claim 22, wherein said Protein C is administered in a concentration of from about 1.0 micrograms per milliliter to about 25.0 micrograms per milliliter.

25. The method of claim 22, wherein said administration of Protein C is selected from the group consisting of topical administration, subconjuctival administration, intracameral injection and intravitreal injection.

26. The method of claim 25, wherein said administration is concurrent with intraocular surgery.

27. The method of claim 26, wherein said intraocular surgery is selected from the group consisting of cataract surgery, vitrectomy, glaucoma filtering procedure, corneal transplantation, and surgery for proliferative vitreoretinopathy.

28. The method of claim 22, further comprising the co-administration of Protein S to an individual having elevated levels of intraocular fibrin.

29. The method of claim 28, wherein said Protein S is administered in a concentration of from about 10 micrograms per milliliter to about 100.0 micrograms per milliliter.